Sustained Viral Response (SVR) Rates in Genotype 1 Treatment-naïve Patients with Chronic Hepatitis C (CHC) Infection Treated with Vaniprevir (MK-7009), a NS3/4a Protease Inhibitor, in Combination with Pegylated Interferon Alfa-2a and Ribavirin for 28 Days

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- I have financial relationships within the last 12 months relevant to my presentation with:

  Astra/Arrows, Boehringer Ingelheim, BMS, Gilead, GlaxoSmithKline, Merck, Novartis, Roche, Schering-Plough, Tibotec and Vertex

  AND

My presentation does include discussion of investigational use of vaniprevir (MK-7009)
MK-7009 007: Phase IIA Study

- **Objective:**
  - Evaluate safety, tolerability and antiviral efficacy of 4 week course of MK-7009 in combination with pegylated interferon 2a and ribavirin (peg-IFN/RBV)

- **Population**
  - Treatment naïve, non-cirrhotic, HCV genotype 1 patients
  - Baseline HCV RNA ≥ 4 x 10^5 IU/mL

- **Overall Design**
  - randomized, placebo-controlled, double-blind, dose-ranging
  - MK-7009 was administered for 28 days with peg-IFN/RBV in 1 of 5 regimens: placebo, 300 mg bid, 600 mg bid, 600 mg qd, or 800 mg qd
Study Design

Primary hypothesis: RVR rates for at least 1 MK-7009-treated group superior to control
Selected Methods

- Safety assessments
  - Serious adverse events (SAEs) collected throughout; non-serious AEs were prompted for through day 42 only
  - Laboratory and ECG assessments

- HCV RNA assessment: Roche Cobas TaqMAN 2.0
  - Limit of quantitation (LOQ): 25 IU/mL
  - Limit of detection (LOD): 10 IU/mL

- IL-28β genotype analysis: Gentris assay
# Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MK-7009 300 mg bid + P+ R (N=18)</th>
<th>MK-7009 600 mg bid + P+ R (N=20)</th>
<th>MK-7009 600 mg qd + P+ R (N=18)</th>
<th>MK-7009 800 mg qd + P+ R (N=19)</th>
<th>Placebo + P+ R (N=19)</th>
<th>Total (N=94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female %</td>
<td>22</td>
<td>45</td>
<td>61</td>
<td>38</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Median Age</td>
<td>46 y</td>
<td>44 y</td>
<td>51 y</td>
<td>44 y</td>
<td>46 y</td>
<td>45 y</td>
</tr>
<tr>
<td>Age Range</td>
<td>27 to 65 y</td>
<td>22 to 58 y</td>
<td>34 to 64 y</td>
<td>21 to 65 y</td>
<td>32 to 65 y</td>
<td>21 to 65 y</td>
</tr>
<tr>
<td>Race: Asian %</td>
<td>6</td>
<td>5</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Black %</td>
<td>11</td>
<td>15</td>
<td>11</td>
<td>5</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Multi-Racial %</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Pacific Islander%</td>
<td>6</td>
<td>-</td>
<td>6</td>
<td>-</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>White %</td>
<td>78</td>
<td>80</td>
<td>72</td>
<td>84</td>
<td>63</td>
<td>76</td>
</tr>
<tr>
<td>HCV Genotype (GT) 1a %</td>
<td>33</td>
<td>40</td>
<td>39</td>
<td>42</td>
<td>42</td>
<td>39</td>
</tr>
<tr>
<td>HCV GT 1b %</td>
<td>50</td>
<td>45</td>
<td>44</td>
<td>37</td>
<td>47</td>
<td>44</td>
</tr>
<tr>
<td>HCV GT1 nontypeable %</td>
<td>17</td>
<td>15</td>
<td>17</td>
<td>21</td>
<td>11</td>
<td>16</td>
</tr>
</tbody>
</table>
HCV RNA Responses at Week 4 (RVR) and Week 12 (cEVR)

<table>
<thead>
<tr>
<th>MK-7009 Dose group</th>
<th>RVR (Full Analysis Set)</th>
<th>% RVR</th>
<th>P value (vs. pbo)</th>
<th>cEVR (Full Analysis Set)</th>
<th>% cEVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg bid</td>
<td>12/18</td>
<td>67</td>
<td>&lt;0.001</td>
<td>14/18</td>
<td>78</td>
</tr>
<tr>
<td>600 mg bid</td>
<td>16/20</td>
<td>80</td>
<td>&lt;0.001</td>
<td>17/20</td>
<td>85</td>
</tr>
<tr>
<td>600 mg qd</td>
<td>12/17</td>
<td>71</td>
<td>&lt;0.001</td>
<td>14/18</td>
<td>78</td>
</tr>
<tr>
<td>800 mg qd</td>
<td>16/19</td>
<td>84</td>
<td>&lt;0.001</td>
<td>14/19</td>
<td>74</td>
</tr>
<tr>
<td>placebo</td>
<td>1/19</td>
<td>5</td>
<td>n/a</td>
<td>9/19</td>
<td>47</td>
</tr>
</tbody>
</table>

- All of the MK-7009 dose groups had superior RVR to control (p< 0. 001), satisfying the primary efficacy hypothesis.
- The proportion of subjects with undetectable virus generally increased during the peg-IFN/RBV phase from week 4 (67-84%) to week 12 (74-85%)
HCV RNA Responses at Week 4 (RVR) and 72 (SVR)

<table>
<thead>
<tr>
<th>MK-7009 Dose group</th>
<th>RVR (Full Analysis Set)</th>
<th>% RVR</th>
<th>SVR (Full Analysis Set)</th>
<th>% SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg bid</td>
<td>12/18</td>
<td>67</td>
<td>11/18</td>
<td>61</td>
</tr>
<tr>
<td>600 mg bid</td>
<td>16/20</td>
<td>80</td>
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<td>16/19</td>
<td>84</td>
<td>16/19</td>
<td>84</td>
</tr>
<tr>
<td>placebo</td>
<td>1/19</td>
<td>5</td>
<td>12/19</td>
<td>63</td>
</tr>
</tbody>
</table>

- SVR for QD and high BID doses of MK7009 numerically higher than placebo
  - Placebo SVR rate higher than expected/historical rate
Population sequencing of NS3/4A gene was performed on subjects with HCV RNA >1000 IU/ml through day 42 of the study.
- Clonal sequencing of the NS3 region was performed on subjects with HCV RNA >1000IU/ml through week 24 of the study

Variants detected at positions 155 and 168
- Consistent with published resistance variants for other NS3/4A protease inhibitors

Figure from Manns et al., 2007 Nat Rev Drug Disc.
No serious adverse events (SAEs) and no discontinuations due to an adverse event were observed during the first 42 days; no MK-7009-related SAEs throughout the study.

The most common adverse events reported were headache, nausea, vomiting, fatigue, and influenza-like illness.
- The incidence of vomiting with MK-7009 600 mg BID was higher than placebo.
- Vomiting was mild-moderate in severity, and did not lead to discontinuation of MK-7009.

No increase in rash adverse events over placebo were observed.

No changes from baseline ECG were observed.

Changes in laboratory values were as expected for peg-IFN/RBV.
- No significant elevations in bilirubin associated with MK-7009.
Conclusions

- Addition of vaniprevir for 28 days to peg-IFN/RBV led to significantly increased RVR for all doses and numerically greater SVR rates for the majority of vaniprevir dose groups.

- Vaniprevir is well-tolerated when given in combination with peg-IFN/RBV.
  - No dose-limiting toxicity observed

A Phase IIIB study of vaniprevir + peg-IFN/RBV in treatment-experienced subjects is ongoing
Acknowledgements

- Special acknowledgement to the study participants, the clinical sites and the scientific and operational support staff who made this study possible.
Participating Study Centers

- Yacov Baruch, MD – Liver Unit_Rambam Healthcare Campus, Haifa, Israel
- Yves Benhamou, MD – Hôpital Pitié-Salpêtrière, Paris, France
- Matthew Cave, MD – University of Louisville Hospital, Louisville, KY
- Gary Davis, MD – Baylor University Medical Center, Dallas, TX
- Shaban Faruqui, MD – Gulf Coast Research LLC, Baton Rouge, LA
- Michael Fried, MD – University of North Carolina at Chapel Hill, Chapel Hill, NC
- Edward Gane, MD – Auckland Clinical Studies, Auckland, New Zealand
- Eliot Godofsky, MD – University Hepatitis Center at Bach and Godofsky, MD, Sarasota, FL
- Michael Gschwantler, MD – Wilhelminenspital, 4. Medizinische Abteilung, Wien, Austria
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- Ming-Yang Lai, MD – National Taiwan University Hospital, Taipei Jhongjheng, Taiwan
- Eric Lawitz, MD – Alamo Medical Research, San Antonio, TX
- Yoav Lurie, MD – Gastrointestinal & Liver Disease Unit_Sourasky MC, Tel Aviv, Israel
- Michael Manns, MD – Hannover Medical School, Hannover, Germany
- Patrick Marcellin, MD – Hôpital Beaujon, Clichy, France
- Darius Moradpour, MD – Centre Hospitalier Universitaire Vaudois, Lausanne VD, Switzerland
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- Maribel Rodriuez-Torres, MD – Fundación de Investigación De Diego, Santurce, Puerto Rico
- Mark Russo, MD – Carolinas Medical Center, Charlotte, NC
- Rifaat Safadi, MD – Liver Unit_Italian (Holy Family) Hospital, Nazareth, Israel
- Alejandro Soza, MD – Hospital de la Pontificia Universidad Catolica, Hepatologia, Santiago Region Metropolitana, Chile
- Ulrich Spengler, MD – Rheinische Friedrich-Wilhelms-Universitaet Bonn, Bonn, Germany
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- Chau-Ting Yeh, MD – Chang Gung Medical Center, Taipei, Taiwan
- Stefan Zeuzem, MD – Klinikum der Johann-Wolfgang-Goethe-Universitaet, Frankfurt, Germany
Scientific and Operational Support

- Janice K. Albrecht
- Joann Brunhofer
- Luzelena Caro
- Tom Chambers
- Michael Chastain
- Ralph DiCampli
- Nancy Fernandez
- Jacqueline Gress
- Robin Isaacs
- Gabriela Ramos
- Joan Saalfrank
- Amha Tadesse
- Robert Tipping
- Janice Wahl
- Amelia Warner
- Wendy Williams
- Hamish Wright